

CLAIMS

1. A method to destroy or impair target cells in a mammalian subject, comprising the steps of:

5 (a) administering to the subject a therapeutically effective amount of a targeted photosensitizer compound having a characteristic light absorption waveband, said targeted photosensitizer compound selectively binding with the target cells, but not binding with non-target cells, said photosensitizer compound being inert upon administration;

10 (b) transcutaneously irradiating at least a portion of the mammalian subject in which the target cells to which the targeted photosensitizer compound has bound is disposed, with light having a waveband corresponding at least in part to the characteristic light absorption waveband of said targeted photosensitizer compound; and

15 (c) ensuring that an intensity of the light used for the step of transcutaneously irradiating is substantially less than  $500 \text{ mw/cm}^2$ , and that a total fluence of the light used for irradiating is sufficiently high to activate said targeted photosensitizer compound, said light activating the targeted photosensitizer compound, causing said target cells to be destroyed or impaired.

20 2. The method of claim 1, further comprising the step of allowing sufficient time for any targeted photosensitizer compound that is not bound to the target cells to clear from the non-target cells of the mammalian subject prior to the step of irradiating.

5 3. The method of claim 1, wherein the target cells are comprised in a target tissue selected from the group consisting of: a vascular endothelial tissue, an abnormal vascular wall of a tumor, a solid tumor, a tumor of a head, a tumor of a neck, a tumor of a gastrointestinal tract, a tumor of a liver, a tumor of a breast, a tumor of a prostate, a tumor of a lung, a nonsolid tumor, malignant cells of one of a hematopoietic tissue and a lymphoid tissue, lesions in a vascular system, a diseased bone marrow, and diseased cells in which the disease is one of an autoimmune and an inflammatory disease.

10 4. The method of claim 3, wherein the target tissue is a lesion of a type selected from the group consisting of atherosclerotic lesions, arteriovenous malformations, aneurysms, and venous lesions.

15 5. The method of claim 1, wherein the step of irradiating comprises the step of providing a light source that is disposed internal to an intact skin layer of the mammalian subject and wherein said light source is activated to produce the light.

20 6. The method of claim 5, wherein the step of irradiating comprises providing a light source that is disposed external to an intact skin layer of the mammalian subject and wherein said light source is activated to produce the light.

7. The method of claim 1, wherein the photosensitizer compound comprises one of:

20 (a) a targeted photosensitizing agent;

(b) a photosensitizing agent delivery system that delivers the targeted photosensitizing agent to bind with the target cells; and

5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

(c) a prodrug that produces a prodrug product, said prodrug product selectively binding to the target cells.

8. The method of claim 7, wherein said photosensitizing agent is conjugated to a ligand that specifically binds to the target cells and that is selected from the group consisting of: an antibody, or bindable fragment thereof; a peptide; a polymer; a glycoprotein; and a lipoprotein.

9. The method of claim 7, wherein said photosensitizer compound is selected from the group consisting of indocyanine green, methylene blue, toluidine blue, aminolevulinic acid, chlorins, phthalocyanines, porphyrins, purpurins, and texaphyrins.

10. The method of claim 1, wherein the step of irradiating is carried out for a time interval of from about 4 minutes to about 72 hours.

11. The method of claim 1, wherein the step of irradiating is carried out for a time interval of from about 60 minutes to about 48 hours.

12. The method of claim 1, wherein the step of irradiating is carried out for a time interval of from about 2 hours to about 24 hours.

13. The method of claim 1, wherein the total fluence of the light used for irradiating is between about 30 Joules and about 25,000 Joules.

14. The method of claim 1, wherein the total fluence of the light used for irradiating is between about 100 Joules and about 20,000 Joules.

15. The method of claim 1, wherein the total fluence of the light used for irradiating is between about 500 Joules and about 10,000 Joules.

5 16. A method for transcutaneously and selectively destroying or impairing target tissue in a mammalian subject, comprising the steps of:

(a) administering to the mammalian subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or an antibody fragment, wherein said antibody or said antibody fragment selectively binds to an antigen of the target tissue, said first conjugate being inert upon administration;

10 (b) administering to the mammalian subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair, conjugated to a photosensitizer compound, said second conjugate being inert upon administration; and

15 (c) irradiating at least a portion of the mammalian subject in which the target tissue that is bound to said antibody or said antibody fragment is disposed, using light having a waveband corresponding at least in part to the characteristic light absorption waveband of said photosensitizer compound, thereby activating said photosensitizer compound and destroying or impairing said target tissue.

20 17. The method of claim 16, wherein the ligand-receptor binding pair is selected from the group consisting of: biotin-streptavidin, chemokine-chemokine receptor, growth factor-growth factor receptor, and antigen-antibody.

25 18. A method for transcutaneously destroying or impairing a target tissue in a mammalian subject, comprising the steps of:

(a) administering to the subject a therapeutically effective amount of an energy activated delivery system, wherein said system comprises an energy activated agent that absorbs energy and destroys a target tissue to which it is bound

5 which is inert upon administration; and a ligand conjugated to said energy activated agent, said ligand binding to a receptor on the target tissue with specificity, so that binding of the ligand to a non-target tissue is minimized;

(b) irradiating at least a portion of the subject with energy at a wavelength that activates said energy activated agent, whereupon said activated targeted tissue is destroyed or impaired thereby.

10 19. The method of claim 18, wherein said irradiation is substantially less than 500 mW/cm<sup>2</sup>.

15 20. The method of claim 18, wherein the target tissue is selected from the group consisting of: a vascular endothelial tissue; an abnormal vascular wall of a tumor; a solid tumor in one of the head, the neck, the gastrointestinal tract, the liver, the breast, the prostate, and the lung; a nonsolid tumor; malignant cells in hematopoietic tissue; malignant cells in lymphoid tissue; lesions in a vascular system; diseased bone marrow; cells afflicted by an autoimmune; and cells afflicted with an inflammatory disease.

20 21. The method of claim 18, wherein said energy is ultrasound energy.

22. The method of claim 1, wherein the level of activation of said photosensitizing agent or prodrug corresponds, in a linear manner, to the amount of time said photosensitizing agent or prodrug are illuminated.

25 ~~23. The method of claim 22, wherein said activation may be incrementally increased or decreased through the respective increase or decrease in irradiation intensity.~~

~~24. The method of claim 1 wherein said activation may be initiated through initiating irradiation or halted through discontinuing irradiation within a therapeutically reasonable time after the photosensitizing agent or prodrug has been administered but prior to biodegradation of said agent or prodrug.~~

~~25. The method of claim 16, wherein the level of activation of said photosensitizing agent or prodrug corresponds, in a linear manner, to the amount of time said photosensitizing agent or prodrug are illuminated.~~

~~26. The method of claim 25 wherein said activation may be incrementally increased or decreased through the respective increase or decrease in irradiation intensity.~~

~~27. The method of claim 16 wherein said activation may be initiated through initiating irradiation or halted through discontinuing irradiation within a therapeutically reasonable time after the photosensitizing agent or prodrug has been administered but prior to biodegradation of said agent or prodrug.~~

~~28. The method of claim 18, wherein the level of activation of said photosensitizing agent or prodrug corresponds, in a linear manner, to the amount of time said photosensitizing agent or prodrug are illuminated.~~

~~29. The method of claim 28 wherein said activation may be incrementally increased or decreased through the respective increase or decrease in irradiation intensity.~~

~~30. The method of claim 18 wherein said activation may be initiated through initiating irradiation or halted through discontinuing irradiation within a therapeutically reasonable time after the photosensitizing agent or prodrug has been administered but prior to biodegradation of said agent or prodrug.~~

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